ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 3, pp. 352–358. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © I.A. Dvornikova, L.L. Frolova, A.V. Kuchin, I.P.Beletskaya, 2007, published in Zhurnal Organicheskoi Khimii, 2007, Vol. 43, No. 3, pp. 357–362.

Synthesis of New Enantiomeric 1,2-Diamines Containing a Myrtenyl Fragment

I. A. Dvornikova[a], L. L. Frolova[a], A. V. Kuchin[a], and I. P. Beletskaya[b]

[a] *Institute of Chemistry, Komi Research Center, Ural Division, Russian Academy of Sciences, ul. Pervomaiskaya 48, Syktyvkar, 167982 Russia*
e-mail: dvornikova-ia@chemi.komisc.ru

[b] *Faculty of Chemistry, Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia*

Received May 10, 2006

Abstract—Some new bi- and tridentate nitrogen-containing chiral ligands were synthesized on the basis of natural monoterpenoids, (+)- and (–)-myrtenals and (+)-myrtenol. A procedure was proposed for the synthesis of unsymmetrical ligands containing terpenoid and *o*-hydroxyphenyl fragments.

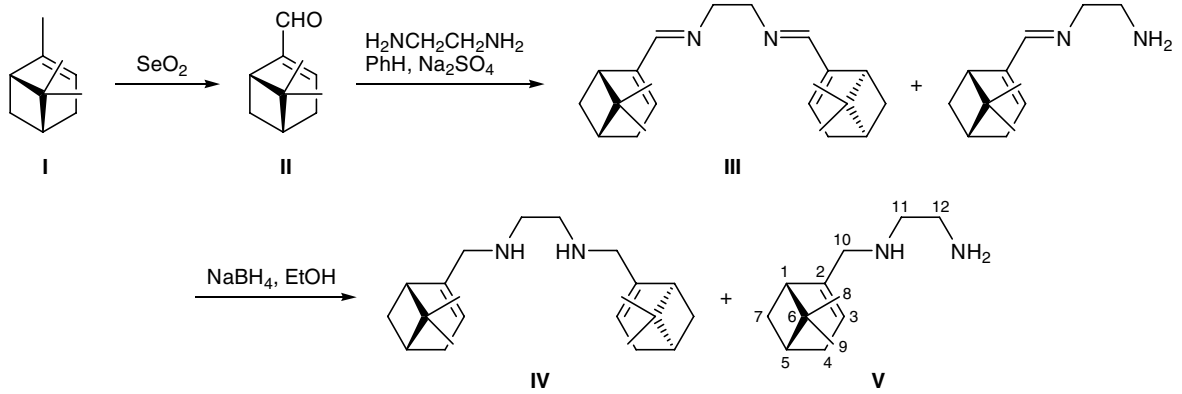
DOI: 10.1134/S1070428007030037

In the recent time, nitrogen-containing ligands have been widely used in organic synthesis, especially in catalytic asymmetric syntheses [1]. Chiral nonracemic 1,2-diamines and their derivatives, such as 1,2-diimines and 1,2-diamides, are used in the alkylation of aldehydes [2, 3], reduction of prochiral ketones [4, 5], oxidation [6, 7], cyclopropanation [8, 9], epoxidation [10, 11], and other reactions. In addition, vicinal diamines are intermediate products in the preparation of heteroelement-containing ring systems [12] and chiral auxiliaries in diastereoselective syntheses [13]. Symmetric 1,2-diamines are used for optical resolution of racemic compounds [14, 15] and determination of enantiomeric purity of chiral compounds by NMR spectroscopy [15, 16]. Despite numerous known 1,2-diamines, new enantiomerically pure ligands are extensively designed. Monoterpenoids, in particular α-pinene and its derivatives, were reported [17–20] as chiral reagents in asymmetric syntheses. Accessibility of both enantiomers of these compounds with an acceptable optical purity makes it possible to obtain promising chiral ligands on their base.

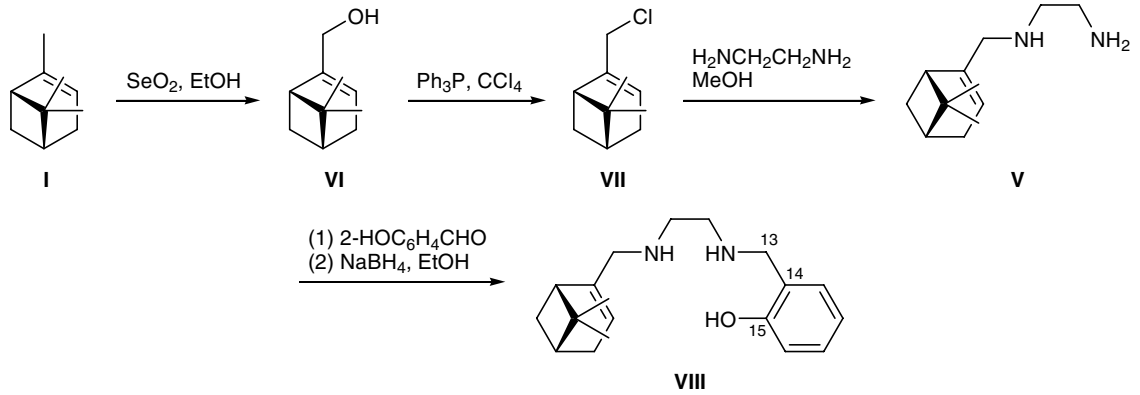
The present article reports on the synthesis of symmetric and several unsymmetrical diamines containing a chiral terpene fragment. As initial terpene compounds we used products of oxidation of α-pinene, myrtenal and myrtenol. The structure of the newly synthesized compounds was determined by ^{1}H and ^{13}C NMR spectroscopy.

Diamine **IV** with a C_2 symmetry was synthesized in two steps. In the first step, (+)-myrtenal (**II**) reacted with 0.5 equiv of ethylenediamine in benzene in the presence of anhydrous Na_2SO_4 to give diimine (+)-**III**,

Scheme 1.



Scheme 2.



and reduction of the latter with $NaBH_4$ in ethanol afforded 69% of diamine (1*S*,5*R*)-**IV** (Scheme 1). The reaction with equimolar amounts of compound **II** and ethylenediamine, apart from the major product (**IV**), gave a small amount of amine **V** which was identified in the reaction mixture by TLC. Dihydrochlorides of **IV** and **V** are characterized by different solubilities, so that they can readily be separated. Diamine (+)-**IV** isolated from the corresponding dihydrochloride contained no impurity of **V**. In the ^{13}C NMR spectrum of **IV** we observed 11 signals; this suggests that the reaction is stereoselective (only one stereoisomer is formed). Likewise, from (–)-myrtenal we obtained the corresponding (1*R*,5*S*)-diamine.

We previously [21] described an analogous reaction with a terpene ketone, 2-hydroxypinan-3-one. Insofar as ketones react with 1,2-diamines much more difficultly, the major product in the reaction with a large excess of ethylenediamine was the corresponding monoimine. In the reaction with aldehydes, initially formed monoimine reacts with the second aldehyde molecule at a considerably higher rate than does the initial diamine. In this case, an appreciable amount of the corresponding diimine may be formed. In fact, the reaction of myrtenal with ethylenediamine even at a ratio of 1:20 gave (after chromatographic separation) 29% of monosubstituted amine **V** and 43% of disubstituted amine **IV**.

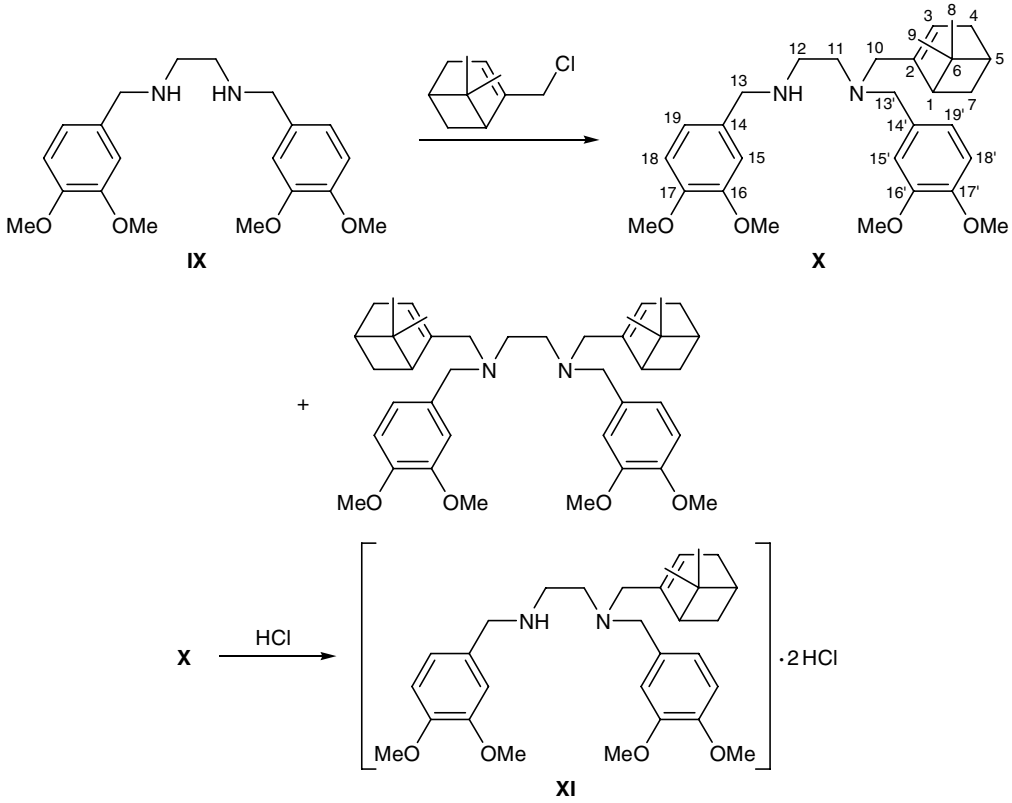
Unsymmetrical diamine **V** was synthesized by alkylation of ethylenediamine with the corresponding halogen derivative. The starting compound was (+)-myrtenol (**VI**) which was obtained by oxidation of (+)-α-pinene (**I**) with selenium(IV) oxide. (+)-Myrtenyl chloride (**VII**) was prepared by treatment of **VI** with triphenylphosphine in carbon tetrachloride following a procedure analogous to that described in [22]. Diamine (+)-**V** was synthesized by reaction of (+)-**VII** with 20 equiv of ethylenediamine in methanol at 60°C. After purification by column chromatography, the yield of (+)-**V** was 77%.

Compound **V** can be used as chiral intermediate for the design of unsymmetrical ligands having different substituents on the nitrogen atoms. The possibility for varying electronic and steric properties of these substituents gives rise to extended scope of application and enhanced efficiency of catalysts derived from the ligands thus obtained. The second substituent can be introduced using, e.g., salicylaldehyde. By condensation of compound **V** with salicylaldehyde, followed by reduction with sodium tetrahydridoborate, we obtained tridentate ligand **VIII** containing phenol and terpene fragments (Scheme 2).

We have synthesized compound **X** as an analog of the known inhibitor of multidrug-resistant tumor cells, SDB-Ethylenediamine [23, 24], in which the open-chain isoprenoid component is replaced by a bicyclic isoprenoid residue. As starting compound we used myrtenyl chloride prepared from α-pinene with an optical purity of ~40%. Analogous *N*,*N*′-disubstituted diamines are also used in asymmetric catalysis [25–27]; therefore, enantiomerically pure unsymmetrical diamine **X** attracts interest as ligand for metal-complex catalysts.

With a view to obtain mainly monoalkylated derivative **X**, the reaction was performed with 4 equiv of *N*,*N*′-bis(3,4-dimethoxybenzyl)ethylenediamine. After separation by column chromatography, the yield of unsymmetrical diamine **X** was 60% (Scheme 3). The ^{13}C NMR spectrum of **X** contained 30 signals, for carbon atoms in the two aromatic fragments are nonequivalent. In the ^{1}H NMR spectrum of **X**, signals belonging to protons in the aromatic and terpene

Scheme 3.



moieties were present. The signal intensity ratio for the aromatic and methyl protons confirmed the structure of **X** as monoalkylated product. The NH signal appeared as a broadened singlet at δ 1.76 ppm.

Preliminary tests showed that the newly synthesized ligands are capable of forming complexes with various metal ions; therefore, they can be used as chiral ligands in asymmetric syntheses. Compound **V** is promising from the viewpoint of obtaining unsymmetrical ligands via reactions with various electrophilic reagents.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM spectrometer at 400.13 and 100.61 MHz, respectively, using $CDCl_3$ as solvent; the chemical shifts were measured relative to the solvent signals (δ 7.24 ppm, δ_C 77.00 ppm). Signals were assigned on the basis of the *J*-modulation ^{13}C NMR spectra and ^{13}C–^{1}H heteronuclear correlation spectra (HETCOR). The IR spectra were obtained on a Specord M-80 spectrometer. The melting points were determined on a Kofler hot stage. The specific rotations were measured at 22°C using a circular CM-3 polarimeter. The purity of initial compounds was checked by GLC on a Ktistall-2000M chromatograph equipped with an HP-5MS quartz capillary column, 60000×0.25 mm, and a flame ionization detector; carrier gas helium. The progress of reactions and the purity of products were monitored by TLC on Silufol and Sorbfil plates using hexane–diethyl ether (0 to 50% of the latter) and chloroform–methanol–concentrated aqueous ammonia (100:10:1) as eluents; spots were visualized by treatment with a solution of vanillin or ninhydrin, followed by heating to 100–120°C, and with a solution of Bromocresol Purple.

(1*S*,5*R*)-(+)-Myrtenal (**II**), $[\alpha]_D$ = +13.3° (neat), and (1*R*,5*S*)-(–)-myrtenal, $[\alpha]_D$ = –10.7° (neat), were prepared by oxidation of (1*R*,5*R*)-(+)-α-pinene (**I**), $[\alpha]_D$ = +42° (neat), and (1*S*,5*S*)-(–)-α-pinene, $[\alpha]_D$ = –42° (neat), respectively, with an equimolar amount of selenium dioxide. Ethylenediamine was boiled and then distilled over metallic sodium.

***N*,*N'*-Bis{[(1*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl]methylidene}ethane-1,2-diamine (III).** A solution of 1.46 g (9.72 mmol) of (1*S*,5*R*)-(+)-myrtenal (**II**) and 0.29 g (4.86 mmol) of ethylenediamine in 15 ml of anhydrous benzene was stirred for 9 h at room temperature in the presence of 9 g of

anhydrous sodium sulfate. The mixture was filtered, the precipitate was washed with benzene, and the solvent was removed from the filtrate under reduced pressure to isolate 1.53 g (97%) of diimine **III**. Yellow semicrystalline material, $[\alpha]_D = -13.7°$ (c = 6.3, $CHCl_3$). IR spectrum (film), ν, cm^{-1}: 1638 (C=N), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 0.74 s (6H, CH_3), 1.05 d (2H, 7-H_β, J = 8.89 Hz), 1.30 s (6H, CH_3), 2.12 m (2H, 5-H), 2.36–2.45 m (6H, 4-H, 7-H_α), 2.89 m (2H, 1-H), 3.70 s (4H, 11-H), 5.92 m (2H, 3-H), 7.65 s (2H, 10-H). ^{13}C NMR spectrum, δ_C, ppm: 20.84 (C^9), 25.80 (C^8), 31.13 (C^4), 32.21 (C^7), 37.49 (C^6), 39.83 (C^5), 40.78 (C^1), 60.94 (C^{11}), 134.31 (C^3), 147.85 (C^2), 163.91 (C^{10}). Found, %: C 81.29; H 10.30; N 8.59. $C_{22}H_{32}N_2$. Calculated, %: C 81.43; H 9.94; N 8.63.

***N*,*N*′-Bis{[(1*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl]methyl}ethane-1,2-diamine (IV).** *a*. A solution of 1.53 g (4.71 mmol) of diimine **III** in 22 ml of ethanol was added under stirring to a solution of 0.36 g (9.43 mmol) of $NaBH_4$ in 16 ml of anhydrous ethanol. The mixture was stirred for 0.5 h on heating, cooled, diluted with 20 ml of water, treated with a 5% solution of sodium hydroxide, and extracted with chloroform. The extract was washed with a saturated aqueous solution of NaCl and dried over K_2CO_3, and the solvent was removed under reduced pressure. The residue, 1.54 g, was dissolved in diethyl ether, and a 2 M solution of hydrogen chloride in alcohol was added to obtain dihydrochloride **IV**·2HCl. Yield 1.46 g (78%), colorless crystals, mp 220°C (from ethanol; decomp.), $[\alpha]_D = +28.3°$ (c = 1.0, EtOH). Found, %: C 65.50; H 9.33; N 6.98. $C_{22}H_{36}N_2$·2HCl. Calculated, %: C 65.82; H 9.54; N 6.98.

Diamine **IV** (base). Slightly yellowish viscous material, yield 1.11 g (69%, calculated on the initial aldehyde), $[\alpha]_D = +34.6°$ (c = 3.8, EtOH). IR spectrum (film), ν, cm^{-1}: 3320 (N–H), 1665 (C=C). ^1H NMR spectrum, δ, ppm: 0.84 s (6H, CH_3), 1.17 d (2H, 7-H_β, J = 8.5 Hz), 1.28 s (6H, CH_3), 1.42 br.s (2H, NH), 2.09 m (4H, 1-H, 5-H), 2.18–2.31 m (4H, 4-H), 2.38 d.t (2H, 7-H_α, J = 8.5, J = 5.6 Hz), 2.69 m (4H, 11-H), 3.11 m (4H, 10-H), 5.36 m (2H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 21.06 (C^9), 26.24 (C^8), 31.19 (C^4), 31.62 (C^7), 38.00 (C^6), 40.99 (C^5), 44.42 (C^1), 48.82 (C^{11}), 54.73 (C^{10}), 117.31 (C^3), 146.81 (C^2).

***N*,*N*′-Bis{[(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl]methyl}ethane-1,2-diamine** was synthesized from (1*R*,5*S*)-(–)-myrtenal as described above for compound **IV**. Yield 72%, $[\alpha]_D = -34.5°$ (c = 1.6, EtOH); dihydrochloride: colorless crystals, mp 221°C (from EtOH; decomp.), $[\alpha]_D = -33.5°$ (c = 1.2, H_2O).

*b. Compounds **IV** and **V** (reaction with excess ethylenediamine).* A solution of 3.11 g (20.7 mmol) of (+)-myrtenal (**II**) and 24.9 g (414.1 mmol) of ethylenediamine in 30 ml of anhydrous benzene was stirred for 9 h at room temperature in the presence of anhydrous sodium sulfate. The inorganic salt was filtered off and washed with benzene, and the solvent and excess ethylenediamine were removed from the filtrate under reduced pressure. The residue, 3.69 g of a mixture of imines, was dissolved in 50 ml of ethanol, the solution was added dropwise to a solution of 0.73 g of $NaBH_4$ in 30 ml of ethanol, and the mixture was stirred for 1 h on heating. The mixture was cooled, diluted with water, treated with a 5% solution of NaOH, and extracted with chloroform. The extract was washed with a saturated aqueous solution of sodium chloride and dried over K_2CO_3, the solvent was removed under reduced pressure, and the residue, 3.65 g of mixture **IV**/**V**, was separated by column chromatography on silica gel (100–250 μm; gradient elution with chloroform–methanol, 1 to 30% of the latter) to isolate 1.57 g (43%) of compound **IV** and 1.06 g (29%) of **V**.

(1*S*,5*R*)-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-3-yl)methanol [VI, (+)-myrtenol]. A solution of 33 g (0.3 mol) of selenium dioxide in 50 ml of ethanol was added over a period of 1 h under stirring to 68 g (0.5 mol) of (+)-α-pinene (**I**) heated to 70–75°C, and the mixture was then stirred for 2 h at that temperature. The mixture was cooled, the precipitate of selenium was filtered off, and the filtrate was subjected to steam distillation to remove volatile products. The organic phase was separated and dried over anhydrous $MgSO_4$. We thus obtained 44.2 g (65%) of a mixture containing (according to the GLC data), 16% of unreacted α-pinene (**I**), 29% of myrtenol (**VI**), and 35% of myrtenal (**II**). This mixture was added under stirring to a solution of 1.9 g (0.05 mol) of $NaBH_4$ in 100 ml of ethanol, and the mixture was stirred until compound **II** disappeared (TLC). Dilute hydrochloric acid was added to the mixture to decompose excess $NaBH_4$, and the mixture was diluted with water and extracted with diethyl ether. The extract was washed with water, dried over $MgSO_4$, and the residue, 38.5 g (87%) of a mixture containing 63% of pyrtenol (GLC), was separated by fractional distillation under reduced pressure. Yield of (+)-myrtenol (**VI**) 21.8 g (32%, calculated on the initial α-pinene), bp 103–105°C (13 mm); n_D^{20} =

1.4960, $[\alpha]_D$ = +48.5° (*c* = 14.8, EtOH); published data [28]: $[\alpha]_D$ = +44.3° (*c* = 3.21, $CHCl_3$). IR spectrum (film), ν, cm^{-1}: 3350 (O–H), 1660 (C=C). ^1H NMR spectrum, δ, ppm: 0.82 s (3H, CH_3), 1.17 d (1H, 7-H_β, *J* = 8.7 Hz), 1.28 s (3H, CH_3), 1.84 br.s (1H), 2.11 d.d (2H, *J* = 1.1, *J* = 5.6 Hz), 2.26 m (2H), 2.39 m (1H), 3.96 m (2H, 10-H), 5.45 t (1H, 3-H, *J* = 1.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.1 (C^9), 26.2 (C^8), 31.1 (C^7), 31.6 (C^4), 37.9 (C^6), 41.0 (C^5), 43.4 (C^1), 65.9 (C^{10}), 117.7 (C^3), 147.9 (C^2).

(1*S*,5*R*)-2-(Chloromethyl)-6,6-dimethylbicyclo-[3.1.1]hept-2-ene [VII, (+)-myrtenyl chloride]. A solution of 2.28 g (14.98 mmol) of (+)-myrtenol (**VI**) and 4.32 g (16.47 mmol) of triphenylphosphine in 16 ml of carbon tetrachloride was heated for 6 h under reflux. The mixture was cooled to room temperature, the precipitate of triphenylphosphine oxide was filtered off and washed with hexane, the solvent was removed from the filtrate under reduced pressure, hexane was added to the residue, and the precipitate of Ph_3PO was filtered off again. The filtrate was partially evaporated, and the residue was passed through a thin layer of silica gel. Removal of the solvent gave 2.15 g (84%) of compound **VII** as a colorless oily liquid, n_D^{20} = 1.4952, $[\alpha]_D$ = +37.9° (*c* = 3.1, EtOH; published data [29]: n_D^{20} = 1.4954. IR spectrum (film), ν, cm^{-1}: 1665 (C=C), 705 (C–Cl). ^1H NMR spectrum, δ, ppm: 0.83 s (3H, CH_3), 1.17 d (1H, 7-H_β, *J* = 8.0 Hz), 1.30 s (3H, CH_3), 2.07–2.55 m (5H), 3.96 m (2H, 10-H), 5.59 m (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 21.42 (C^9), 26.42 (C^8), 31.54 (C^4), 31.84 (C^7), 38.34 (C^6), 40.95 (C^5), 44.76 (C^1), 48.16 (C^{10}), 122.22 (C^3), 144.67 (C^2).

***N*-{[(1*S*,5*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl]methyl}ethane-1,2-diamine (V).** A solution of 1.51 g (8.85 mmol) of compound **VII** and 10.63 g (176.93 mmol) of ethylenediamine in 30 ml of methanol was stirred for 3 h at 55–60°C. The solvent and most part of excess ethylenediamine were removed under reduced pressure, the residue was treated with 2 M hydrochloric acid, the resulting solution was washed with diethyl ether, and the organic extracts were discarded. The aqueous phase was treated with a 5% solution of sodium hydroxide and extracted with diethyl ether. The extract was washed with a saturated aqueous solution of sodium chloride and dried over K_2CO_3, the solvent was removed under reduced pressure, and the residue was subjected to chromatography on silica gel (gradient elution with chloroform–methanol, 1 to 30% of the latter). Yield 1.32 g (77%), yellowish oily liquid, $[\alpha]_D$ = +23.9° (*c* = 5.3, EtOH). IR spectrum (film), ν, cm^{-1}: 3300 br (N–H), 1665 (C=C). ^1H NMR spectrum, δ, ppm: 0.84 s (3H, CH_3), 1.17 d (1H, 7-H_β, *J* = 8.5 Hz), 1.28 s (3H, CH_3), 1.59 br.s (3H, NH, NH_2), 2.09 m (2H, 1-H, 5-H), 2.17–2.32 m (2H, 4-H), 2.38 d.t (1H, 7-H_α, *J* = 8.5, *J* = 5.6 Hz), 2.63–2.66 m (2H, 11-H), 2.78–2.81 m (2H, 12-H), 3.12 m (2H, 10-H), 5.37 m (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 21.01 (C^9), 22.60 (C^8), 31.13 (C^4), 31.56 (C^7), 37.96 (C^6), 40.92 (C^5), 41.68 (C^{12}), 44.38 (C^1), 51.87 (C^{11}), 54.60 (C^{10}), 117.40 (C^3), 146.65 (C^2). Dihydrochloride **V**·2HCl, mp 200–202°C (from propan-2-ol; decomp.), $[\alpha]_D$ = +18.6° (*c* = 1.8, ethanol). Found, %: C 53.68; H 8.94; N 10.34. $C_{12}H_{22}N_2\cdot 2HCl$. Calculated, %: C 53.93; H 9.05; N 10.48.

(1*S*,5*R*)-2-{2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethylamino)ethylaminomethyl}phenol (VIII). A solution of 0.3 g (1.54 mmol) of diamine **V** and 0.19 g (1.54 mmol) of salicylaldehyde in 5 ml of anhydrous methanol was stirred for 6 h at ~20°C. The solvent was removed under reduced pressure, the residue, 0.46 g, was dissolved in 10 ml of ethanol, the resulting solution was added dropwise to a solution of 0.12 g of $NaBH_4$ in 5 ml of ethanol, and the mixture was stirred for 1 h on heating. The mixture was cooled, diluted with water, treated with a 5% solution of sodium hydroxide, and extracted with chloroform. The organic extract was washed with a saturated aqueous solution of sodium chloride and dried over K_2CO_3, the solvent was removed under reduced pressure, the residue was treated with diethyl ether, and the colorless precipitate was filtered off. Yield 0.27 g (59%), mp 107–109°C, $[\alpha]_D$ = +14.4° (*c* = 0.4, $CHCl_3$). IR spectrum (KBr), ν, cm^{-1}: 3430, 3300, 2917,1665, 1582, 1489, 1420, 1264, 758. ^1H NMR spectrum, δ, ppm: 0.83 s (3H, CH_3), 1.15 d (1H, 7-H_β, *J* = 8.6 Hz), 1.28 s (3H, CH_3), 2.07–2.09 m (2H, 1-H, 5-H), 2.19–2.31 m (2H, 4-H), 2.38 d.t (1H, 7-H_α, *J* = 8.5, *J* = 5.6 Hz), 2.71–2.78 m (4H, 11-H, 12-H), 3.10 m (2H, 10-H), 4.00 s (2H, 13-H), 5.35 m (1H, 3-H), 6.76 t.d (1H, H_{arom}, *J* = 7.6, *J* = 1.2 Hz), 6.82 d (1H, H_{arom}, *J* = 8.0 Hz), 6.98 d (1H, H_{arom}, *J* = 6.8 Hz), 7.14 t.d (1H, H_{arom}, *J* = 7.8, *J* = 2.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.09 (C^9), 26.23 (C^8), 31.21 (C^4), 31.64 (C^7), 38.04 (C^6), 40.95 (C^5), 44.35 (C^1), 47.88 (C^{12}), 48.13 (C^{11}), 52.53 (C^{13}), 54.58 (C^{10}), 116.35 (CH_{arom}), 117.91 (C^3), 118.86 (CH_{arom}), 122.59 (C^{14}), 128.26 (CH_{arom}), 128.60 (CH_{arom}), 146.48 (C^2), 158.35 (C^{15}). Found, %: C 73.20; H 9.00; N 9.00. $C_{19}H_{28}N_2O$. Calculated, %: C 75.96; H 9.39; N 9.32.

***N*,*N′*-Bis(3,4-dimethoxybenzyl)ethane-1,2-diamine (IX)** was synthesized from 3,4-dimethoxybenzaldehyde and ethylenediamine in the presence of $NaBH_4$ according to the known procedure [30]. After recrystallization from diethyl ether, yield 72%. ^{1}H NMR spectrum, δ, ppm: 1.65 br.s (2H, NH), 2.76 s (4H, CH_2), 3.72 s (4H, CH_2), 3.86 s and 3.87 s (6H each, OCH_3), 6.79–6.87 m (6H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 48.72, 53.66, 55.74, 55.84, 110.92, 111.27, 120.07, 133.08, 147.90, 148.87.

***N*,*N′*-Bis(3,4-dimethoxybenzyl)-*N*-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-ylmethyl)ethane-1,2-diamine (X).** A solution of 0.72 g (4.2 mmol) of compound **VII** in 30 ml of methanol was added dropwise over a period of 2.5 h to a solution of 6.08 g (16.9 mmol) of diamine **IX** in 30 ml of methanol under stirring at room temperature. The mixture was heated to 60°C and stirred for 4 h at that temperature. The solvent was removed under reduced pressure, the residue was dissolved in chloroform, and the solution was treated with a saturated aqueous solution of K_2CO_3. The aqueous phase was extracted with chloroform, the organic extracts were dried over K_2CO_3 and evaporated under reduced pressure, the residue was treated with hexane, and (after a time) the precipitate of unreacted diamine **IX** was filtered off. The hexane solution was evaporated, and the residue, 1.96 g, containing reaction products and a small amount of the initial diamine was subjected to column chromatography on silica gel using chloroform and chloroform–methanol (100:1) as eluents. Yield 1.33 g (68%). Colorless oily substance. IR spectrum (film), ν, cm^{-1}: 3320, 2944, 2840, 1660, 1612, 1596, 1520, 1468, 1422, 1368, 1266, 1238, 1158, 1112, 1032, 810, 758, 668. ^{1}H NMR spectrum, δ, ppm: 0.82 s (3H, CH_3), 1.17 d (1H, 7-H$_\beta$, J = 8.5 Hz), 1.27 s (3H, CH_3), 1.79 br.s (1H, NH), 2.10 m (1H), 2.20–2.31 m (3H), 2.35–2.40 m (1H), 2.46–2.52 m (1H), 2.59–2.73 m (3H), 2.86–2.96 m (2H), 3.35 d (1H, J = 13.6 Hz), 3.55–3.60 m (3H), 3.76 s (3H, OCH_3), 3.85 s (3H, OCH_3), 3.86 s (3H, OCH_3), 3.87 s (3H, OCH_3), 5.42 br.s (1H, =C**H**–CH_2), 6.75–6.84 m (6H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.16 (CH_3); 26.38 (CH_3); 31.39 (C^4); 31.82 (C^7); 37.97 (C^6); 40.91 (C^5); 44.48 (C^1); 46.87 (C^{12}); 53.23, 53.79 (C^{13}, $C^{13'}$); 55.62, 55.85, 55.91, 55.95 (OCH_3); 58.14, 60.24 (C^{11}, C^{10}); 110.82, 111.01 (C^{15}, $C^{15'}$); 111.41, 111.77 (C^{18}, $C^{18'}$); 119.97, 120.07, 120.72 (C^{19}, $C^{19'}$, C^3); 132.66, 133.27 (C^{14}, $C^{14'}$); 146.37 (C^2); 147.87, 147.96 (C^{17}, $C^{17'}$); 148.86, 148.95 (C^{16}, $C^{16'}$). Dihydrochloride **XI**·2HCl was obtained by adding a 2 N solution of hydrogen chloride in alcohol to a solution of 1.25 g of diamine **XI** in diethyl ether. Yield 1.03 g (72%), colorless amorphous substance. Found, %: C 63.10; H 7.47; N 4.76. $C_{30}H_{42}N_2O_4 \cdot 2HCl$. Calculated, %: C 63.48; H 7.81; N 4.94.

This study was performed under financial support by the INTAS International Research Center (grant no. 99-1541) and by the Russian Foundation for Basic Research (project no. 00-03-40139)

REFERENCES

1. Fache, F., Schulz, E., Tommasino, M.L., and Lemaire, M., *Chem. Rev*., 2000, vol. 100, p. 2159.
2. Belokon, Y.N., North, M., and Parsons, T., *Org. Lett*., 2000, p. 1617.
3. Yoshioka, M., Kawakita, T., and Ohno, M., *Tetrahedron Lett*., 1989, vol. 30, p. 1657.
4. Mukaiyama, T., Tomimori, K., and Oriyama, T., *Chem. Lett*., 1985, p. 813.
5. Tommasino, M.L., Thomazeau, C., Touchard, F., and Lemaire, M., *Tetrahedron: Asymmetry*, 1999, vol. 10, p. 1813.
6. Kokubo, C. and Katsuki, T., *Tetrahedron*, 1996, vol. 52, p. 13895.
7. Adam, W., Fell, R.T., Stegmann, V.R., and Saha-Moller, C.R., *J. Am. Chem. Soc*., 1998, vol. 120, p. 708.
8. Saha, B., Uchida, T., and Katsuki, T., *Tetrahedron: Asymmetry*, 2003, vol. 14, p. 823.
9. Takahashi, H., Yoshioka, M., Shibasaki, M., Ohno, M., Imai, N., and Kobayashi, S., *Tetrahedron*, 1995, vol. 51, p. 12013.
10. Jacobsen, E.N., Zhang, W., Muci, A.R., Ecker, J.R., and Deng, L., *J. Am. Chem. Soc*., 1991, vol. 113, p. 7063.
11. Ito, Y.N. and Katsuki, T., *Bull. Chem. Soc. Jpn*., 1999, vol. 72, p. 603.
12. Korovin, A.V. and Tkachev, A.V., *Izv. Ross. Akad. Nauk, Ser. Khim*., 2001, p. 304.
13. Blazis, V.J., Koeller, K.J., and Spilling, C.D., *Tetrahedron: Asymmetry*, 1994, vol. 5, p. 499.
14. Cucciolito, M.E., Ruffo, F., and Vitagliano, A., *Tetrahedron Lett*., 1994, vol. 35, p. 169.
15. Cucciolito, M.E., Flores, G., and Vitagliano, A., *Organometallics*, 2004, vol. 23, p. 15.
16. Alexakis, A., Frutos, J.C., Mutti, S., and Mangeney, P., *J. Org. Chem*., 1994, vol. 59, p. 3326.
17. Lötcher, D., Rupprecht, S., Stoeckli-Evans, H., and von Zelewsky, A., *Tetrahedron: Asymmetry*, 2000, vol. 11, p. 4341.
18. Cherng, Y.-J., Fang, J.-M., and Lu, T.-J., *J. Org. Chem*., 1999, vol. 64, p. 3207.
19. Irako, N., Hamada, Y., and Shioiri, T., *Tetrahedron*, 1995, vol. 51, p. 12731.

20. Watanabe, M., Awen, B.Z., and Kato, M., *J. Org. Chem.*, 1993, vol. 58, p. 3923.
21. Dvornikova, I.A., Frolova, L.L., Churakov, A.V., and Kuchin, A.V., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2004, p. 1270.
22. Marinetti, A., Buzin, F.-X., and Ricard, L., *J. Org. Chem.*, 1997, vol. 62, p. 297.
23. Suzuki, H., Tomida, A., and Nishimura, T., *Jpn. J. Cancer Res.*, 1990, vol. 81, p. 298.
24. Sidorova, T.A., Nigmatov, A.G., Kakpakova, E.S., Stavrovskaya, A.A., Gerassimova, G.K., Shtil, A.A., and Serebryakov, E.P., *J. Med. Chem.*, 2002, vol. 45, p. 5330.
25. Tshuva, E.Y., Gendeziuk, N., and Kol, M., *Tetrahedron Lett.*, 2001, vol. 42, p. 6405.
26. Berkessel, A., Frauenkron, M., Schwenkreis, T., Steinmetz, A., Baum, G., and Fenske, D., *J. Mol. Catal. A: Chem.*, 1996, vol. 113, p. 321.
27. Fenton, R.R., Stephens, F.S., Vagg, R.S., and Williams, P.A., *Inorg. Chim. Acta*, 1995, vol. 231, p. 73.
28. Harwood, L.M. and Julia, M., *Synthesis*, 1980, p. 456.
29. Tishchenko, D. and Matveev, B., *Zh. Obshch. Khim.*, 1950, vol. 20, p. 896.
30. Akiyama, S.-I., Yoshimura, A., Kikuchi, H., Sumizawa, T., Kuwano, M., and Tahara, Y., *Mol. Pharmacol.*, 1989, vol. 36, p. 730.